ii) the target is bound by the TE but not by the pre-targeted enzyme under like conditions, and the variant sequence was not known to bind to the target independently of the targeted enzyme;[,]

iii) the target is not an isolated monoclonal antibody; [, and]

iv) the variation-tolerant sequence is not in a protein binding domain of the pre-targeted enzyme; and

v) the catalytic activity of the targeted enzyme is greater than 1% of the pre-targeted enzyme.

2. (AMENDED) A targeted enzyme exhibiting a catalytic activity, comprising:

a) a substrate recognition site;

b) a first targeting site that binds a first target; and

c) a second targeting site that binds a second target,

wherein

i) each targeting site comprises a variant sequence, the variant sequence being between 1 and 50 amino acids, the variant sequence being derived from variation-tolerant sequences, wherein the variation-tolerant sequences each comprise a loop, the variation-tolerant sequences being of a corresponding pre-targeted enzyme, [and]

ii) the affinity of the targeted enzyme for the first and second target is greater than the affinity of the pre-targeted enzyme for the first and second target under like conditions, and the variant sequence was not known to bind to the target independently of the targeted enzyme and

iii) the catalytic activity of the targeted enzyme is greater than 1% of the pre-targeted enzyme.

3. (ORIGINAL) The targeted enzyme of Claim 2, wherein the first target and the second target are of a different identity.

4. (ORIGINAL) The targeted enzyme of Claim 2, wherein the first target and second target bind targets of the same identity.

5. (ORIGINAL) The targeted enzyme of Claim 2, wherein at least one of the targeting sites comprises two variant sequences.

6. (ORIGINAL) The targeted enzyme of Claim 5, wherein at least one of the targeting sites comprises three variant sequences.

7. (AMENDED) A targeted enzyme exhibiting a catalytic activity, comprising:

a) a substrate recognition site; and

b) a targeting site that binds a target,

wherein

i) the targeting site comprises two variant sequences, the variant sequences being between 1 and 50 amino acids, the variant sequence being derived from variation-tolerant sequences, wherein the variation-tolerant sequences each comprise a loop, the variation-tolerant sequences being of a corresponding pre-targeted enzyme,

ii) the affinity of the targeted enzyme for the target is greater than the affinity of the pre-targeted enzyme for the target under like conditions, and the variant sequence was not known to bind to the target independently of the targeted enzyme; [, and]

iii) the target is not an isolated monoclonal antibody; and

iv) the catalytic activity of the targeted enzyme is greater than 1% of the pre-targeted enzyme

8. (AMENDED) A targeted enzyme exhibiting a catalytic activity, comprising:

a) a substrate recognition site; and

b) a targeting site that binds a target[.],

wherein

i) the targeting site comprises three variant sequences, the variant sequences being between 1 and 50 amino acids, wherein each of the

variant sequences is derived from variation-tolerant sequences, wherein the variation-tolerant sequences each comprise a loop, the variation-tolerant sequences being of a corresponding pre-targeted enzyme, [and]

ii) the affinity of the targeted enzyme for the target is greater than the affinity of the pre-targeted enzyme for the target under like conditions, and the variant sequence was not known to bind to the target independently of the targeted enzyme, and

iii) the catalytic activity of the targeted enzyme is greater than at least 1% of the pre-targeted enzyme.

9. (AMENDED) The pharmaceutical composition of Claim 1 wherein the [targeted enzyme targeting site] variant-sequence comprises at least two variant sequences [targeted enzyme].

10. (ORIGINAL) The pharmaceutical composition of Claim 1, wherein the targeted enzyme comprises two targeting sites.

11. (ORIGINAL) The pharmaceutical composition of Claim 10, wherein the targeted enzyme targeting sites bind targets of different identities.

Please cancel claim 12.

13. (ORIGINAL) The pharmaceutical composition of Claim 1, wherein the targeted sequence variant sequence is between about 3 and about 20 amino acid residues.

14. (ORIGINAL) The pharmaceutical composition of Claim 1, wherein the targeted enzyme has a molecular weight of less than about 45,000 Daltons.

15. (ORIGINAL) The pharmaceutical composition of Claim 1, wherein the targeted enzyme binds the target with a k_d of about 5 nM or less.

16. (ORIGINAL) The pharmaceutical composition of Claim 1, wherein the targeted enzyme, while bound to target, exhibits a catalytic activity of greater than about 1% relative to the catalytic activity of the pre-targeted enzyme.

17. (ORIGINAL) The targeted enzyme of one of Claims 1, 2, 7 or 8, wherein the pre-targeted enzyme is selected from the group consisting of: proteases, carboxypeptidases, β-lactamases, asparaginases, oxidases, hydrolases, lyases, lipases, cellulases, amylases, kinases, phosphatases, transferases, aldolases and reductases.

18. (ORIGINAL) The pharmaceutical composition of Claim 1, wherein the target is a protein or a cell.

Please cancel claim 22.

23. (AMENDED) A pharmaceutical composition comprising a targeted β-lactamase enzyme and a pharmaceutically acceptable carrier, excipient, or diluent, said enzyme comprising:

a) a substrate recognition site;

b) a targeting site that binds a target; and

c) a sequence KTXS at its substrate recognition site,

wherein

i) the targeting site comprises a variant sequence, the variant sequences being between 1 and 50 amino acids, the variant sequence being [that is] derived from a variation-tolerant sequence, wherein the variation-tolerant sequences each comprise a loop, the variation tolerant sequences being of a corresponding pre-targeted enzyme that does not bind the target,

ii) the target is bound by the targeted β-lactamase enzyme but not by the pre-targeted β-lactamase enzyme under like conditions, and the variant sequence was not known to bind to the target independently of the targeted enzyme, [and]

iii) the target is not an isolated monoclonal antibody and

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iv) the catalytic activity of the targeted enzyme is greater than 1% of the pre-targeted enzyme

24. (AMENDED) A targeted β-lactamase enzyme exhibiting a catalytic activity, comprising:

a) a substrate recognition site;

b) a first targeting site that binds a first target;

c) a second targeting site that binds a second target; and

d) a sequence KTXS at its substrate recognition site,

wherein

i) each targeting site comprises a variant sequence, the variant sequence being between 1 and 50 amino acids, the variant sequence being derived from variation-tolerant sequences, wherein the variation-tolerant sequences each comprise a loop, the variation-tolerant sequences being of a corresponding pre-targeted enzyme, and

ii) the affinity of the targeted enzyme for the first and second target is greater than the affinity of the pre-targeted enzyme for the first and second target under like conditions, and the variant sequence was not known to bind to the target independently of the targeted enzyme.

25. (ORIGINAL) The targeted β-lactamase enzyme of Claim 24, wherein the first target and the second target are of a different identity.

26. (ORIGINAL) The targeted β-lactamase enzyme of Claim 24, wherein the first target and second target bind targets of the same identity.

27. (ORIGINAL) The targeted β-lactamase enzyme of Claim 24, wherein at least one of the targeting sites comprises two variant sequences.

28. (ORIGINAL) The targeted β-lactamase enzyme of Claim 27, wherein at least one of the targeting sites comprises three variant sequences.

29. (AMENDED) A targeted β-lactamase enzyme exhibiting a catalytic activity, comprising:

a) a substrate recognition site;

b) a targeting site that binds a target, and

c) a sequence KTXS at its substrate recognition site,

wherein

i) the targeting site comprises three variant sequences, the variant sequence being between 1 and 50 amino acids, wherein each of the variant sequences is derived from variation-tolerant sequences, wherein the variation-tolerant sequences each comprise a loop, the variation-tolerant sequences being of a corresponding pre-targeted β-lactamase enzyme, [and]

ii) the affinity of the targeted β-lactamase enzyme for the target is greater than the affinity of the pre-targeted β-lactamase enzyme for the target under like conditions, and the variant sequence was not known to bind to the target independently of the targeted enzyme and

ii) the catalytic activity of the targeted enzyme is greater than 1% of the pre-targeted enzyme.

30. (AMENDED) A targeted β-lactamase enzyme exhibiting a catalytic activity, comprising:

a) a substrate recognition site, and

b) a targeting site that binds a target, and

c) a sequence KTXS at its substrate recognition site,

wherein

i) the targeting site comprises two variant sequences, the variant sequeneces being between 1 and 50 amino acids, wherein each of the variant sequences is derived from variation-tolerant sequences, wherein the variation-tolerant sequences each comprise a loop, the variation tolerant sequences being of a corresponding pre-targeted β-lactamase enzyme,

i) the affinity of the targeted β-lactamase enzyme for the target is greater than the affinity of the pre-targeted β-lactamase enzyme for the target, and the variant sequence was not known to bind to the target independently of the targeted enzyme, [and]

iii) the target is not an isolated monoclonal antibody, and

iv) the catalytic activity of the targeted enzyme is greater than 1% of the pre-targeted enzyme

31. (ORIGINAL) The pharmaceutical composition of Claim 23, further comprising a sequence VHKTGSTG.

32. (ORIGINAL) The pharmaceutical composition of Claim 23, wherein the targeting site comprises two variant sequences.

33. (ORIGINAL) The pharmaceutical composition of Claim 23, wherein the targeted β-lactamase enzyme comprises two targeting sites.

34. (ORIGINAL) The pharmaceutical composition of Claim 23, wherein the variation-tolerant sequence is selected from the group consisting of loop A, loop B, loop C, loop D and loop E.